A clinical feasible method for computed tomography-based assessment of sarcopenia In patients with chronic pancreatitis

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Abstract: OBJECTIVES: Sarcopenia is a serious but often overlooked complication of chronic pancreatitis (CP). We investigated the prevalence and risk factors for sarcopenia in patients with CP and determined the utility of a computed tomography (CT)-based method, based on psoas muscle measurements, for easy and clinical feasible diagnosis of sarcopenia. METHODS: This was a retrospective multicenter study of 265 patients with CP. We used segmentation of CT images to quantify skeletal muscle mass and diagnose sarcopenia. On the same CT image as used for muscle segmentation, psoas muscle thickness and cross-sectional area were measured and receiver operating characteristic analyses defined age and sex-specific cutoffs for diagnosing sarcopenia. RESULTS: The prevalence of sarcopenia was 20.4%. The optimal height-adjusted psoas muscle cross-sectional area cutoff for diagnosing sarcopenia was 3.3 cm/m in males and 2.5 cm/m in females. The corresponding area under the receiver operating characteristic curves were 0.8 and 0.9, with sensitivities of 84% and 81% and specificities of 62% and 81%, respectively. Comparable diagnostic performance characteristics were observed for psoas muscle thickness. CONCLUSIONS: Sarcopenia is present in 1 of 5 patients with CP. Assessment of psoas muscle parameters provides a clinical feasible method to diagnose sarcopenia.

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A Clinical Feasible Method for Computed Tomography-Based Assessment of Sarcopenia in Patients With Chronic Pancreatitis

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Objectives: Sarcopenia is a serious but often overlooked complication of chronic pancreatitis (CP). We investigated the prevalence and risk factors for sarcopenia in patients with CP and determined the utility of a computed tomography (CT)-based method, based on psoas muscle measurements, for easy and clinical feasible diagnosis of sarcopenia.

Methods: This was a retrospective multicenter study of 265 patients with CP. We used segmentation of CT images to quantify skeletal muscle mass and diagnose sarcopenia. On the same CT image as used for muscle segmentation, psoas muscle thickness and cross-sectional area were measured and receiver operating characteristic analyses defined age and sex-specific cutoffs for diagnosing sarcopenia.

Results: The prevalence of sarcopenia was 20.4%. The optimal height-adjusted psoas muscle cross-sectional area cutoff for diagnosing sarcopenia was 3.3 cm^2/m^2 in males and 2.5 cm^2/m^2 in females. The corresponding area under the receiver operating characteristic curves were 0.8 and 0.9, with sensitivities of 84% and 81% and specificities of 62% and 81%, respectively. Comparable diagnostic performance characteristics were observed for psoas muscle thickness.

Conclusions: Sarcopenia is present in 1 of 5 patients with CP. Assessment of psoas muscle parameters provides a clinical feasible method to diagnose sarcopenia.

Key Words: sarcopenia, psoas muscle, chronic pancreatitis, computed tomography

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Patients with chronic pancreatitis (CP) are at an increased risk of sarcopenia due to exocrine pancreatic insufficiency, maldigestion, disability, and a number of other risk factors.[1–5] In keeping with findings from other diseases, we recently showed that 1 of 5 CP outpatients had sarcopenia in a tertiary referral center and that the presence of sarcopenia was associated with increased hospitalization rates and mortality.[6] However, most previous studies on sarcopenia have relied on nutritional assessment tools that are not available in a standard clinical setting, which hinder a wider clinical application and routine assessment of sarcopenia.

Computed tomography (CT) is recommended as the first-line imaging modality for the diagnosis and assessment of CP, and as such, most patients will have a CT examination during their clinical workup.[7] In addition, CT is also considered a valuable tool for characterization of body composition and can be used for assessment of skeletal muscle mass.[8] This is achieved by computerized image segmentation of skeletal muscle area normally using axial scans at the lumbar level. Assessment of muscle mass based on CT has been used in a number of different patient groups including CP.[2,9–13] Although this objective approach for the assessment of muscle mass is attractive, it relies on complex computations that are hardly generalizable to a clinical setting. Therefore, more simple CT-based methods for the detection of sarcopenia are needed.

We hypothesized that psoas muscle parameters, measured on standard axial CT images at the fourth lumbar level, could be used to detect sarcopenia. The specific aims of this study were as follows: (*a*) to determine the prevalence of sarcopenia using segmented skeletal muscle area, (*b*) to investigate risk factors associated with sarcopenia, and (*c*) to derive cutoff value of psoas muscle thickness and psoas muscle cross-sectional area (CSA) for the diagnosis of sarcopenia using segmented skeletal muscle area as the reference method.

MATERIALS AND METHODS

This was a retrospective multicenter study including CP outpatients from 3 tertiary referral centers. All clinical, biochemical, and imaging examinations were obtained during routine clinical workup, and consequently, the informed consent requirement was waived in agreement with directions from the ethic committees at the participating institutions. Approvals for data collection and storage were obtained from national data protection agencies.

Patient Population

Consecutive adult patients (age >18 years) with a diagnosis of CP having a CT examination between January 2011 and March 2018 were eligible for the study. Cases were retrospectively identified through review of medical records; the M-ANNHEIM criteria were used to establish the diagnosis of CP.[14] Exclusion criteria were (*a*) patients with a CT scan of inadequate quality for skeletal muscle mass segmentation, (*b*) patients with no registration of height at the time of CT examination, (*c*) patients with incomplete information on disease characteristics, and (*d*) patients with active cancer or signs of decompensated chronic liver disease.

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Demographic and Disease Characteristics

Information on patients' demographic and disease characteristics including age, sex, etiology of CP, use of opioid based pain medication, and the presence of diabetes and pancreatic calcifications was recorded in standardized case report forms. No formal testing of the patients' exocrine pancreatic function was undertaken on the day of CT examination, and consequently, pancreatic enzyme replacement therapy (PERT) was used as an indication of exocrine pancreatic insufficiency.

Psoas Muscle Measurements and Segmentation of Body Composition

Standard CT abdominal image sets were obtained in all included patients according to local protocols at the participating institutions. All CT examinations were performed for the purpose of clinical investigations, typically with a slice thickness of 2 mm. Computed tomography images without venous or arterial phases contrast enhancement were used for the segmentation process.

Psoas muscle measurements were performed on a single axial CT slice corresponding to the mid-level of the fourth lumbar vertebra.[15] Psoas muscle thickness was measured as the 2-point transverse (lateral to lateral) diameter, and the CSA of the psoas muscle was determined by manual encircling the outer surface of the muscle (Fig. 1). All measurements were performed on the right psoas muscle using the picture archiving and communication systems at the participating institutions. Psoas muscle thickness was normalized to stature by division by height and psoas muscle CSA by height squared.[9,13]

Body composition analysis was performed using the Viking Slice software, which has previously been validated for assessment of body composition in patients with CP. A detailed description of the methodology has been published elsewhere.[15] In brief, the method is based on the attenuation (Hounsfield units) on CT images. Adipose tissue and skeletal muscle CSAs were assessed using standard definitions of HU threshold (for adipose tissue: −190 to −30 HU and for skeletal muscle: −29 to 150 HU). Regions of interest included measurement of subcutaneous adipose tissue, visceral adipose tissue, intramuscular adipose tissue, and skeletal muscle on the fourth vertebral level. For the present study, only skeletal muscle assessments were used. To normalize the skeletal muscle CSA to stature, a skeletal muscle index (SMI) was calculated as the skeletal muscle CSA (square centimeter) divided by height squared (square meter).[16]

Definition of Sarcopenia

Sarcopenia was defined according to recent published SMI cutoff values for sarcopenia diagnosis based on more than 700 healthy individuals.[16] Sex-specific cutoff values for the fourth vertebral level based on 2 standard deviations (SD) below group means were used:

- Female: SMI <34.2 cm^2/m^2
- Male: SMI <41.3 cm^2/m^2

Statistical Analysis

All data are reported as mean (SD) or numbers (%), unless otherwise indicated. Univariate and stepwise multivariate logistic regression with backward elimination (P value threshold <0.2) was used for analysis of the association between sarcopenia, demographics, and disease characteristics. Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Associations between psoas muscle thickness, psoas muscle CSA, and the presence of sarcopenia were investigated using Pearson correlation coefficients and Student t test. The diagnostic accuracy, sensitivity, specificity, and posttest probabilities (likelihood ratios [LRs]) of psoas muscle assessment parameters for diagnosing sarcopenia were calculated using area under the receiver operating characteristics curve. Sex-specific optimal cutoff values were determined by maximizing the Youden index. Prediction plots were constructed from logistic regression models with psoas muscle thickness as continuous predictor. P values of less than 0.05 were considered significant. The software package STATA

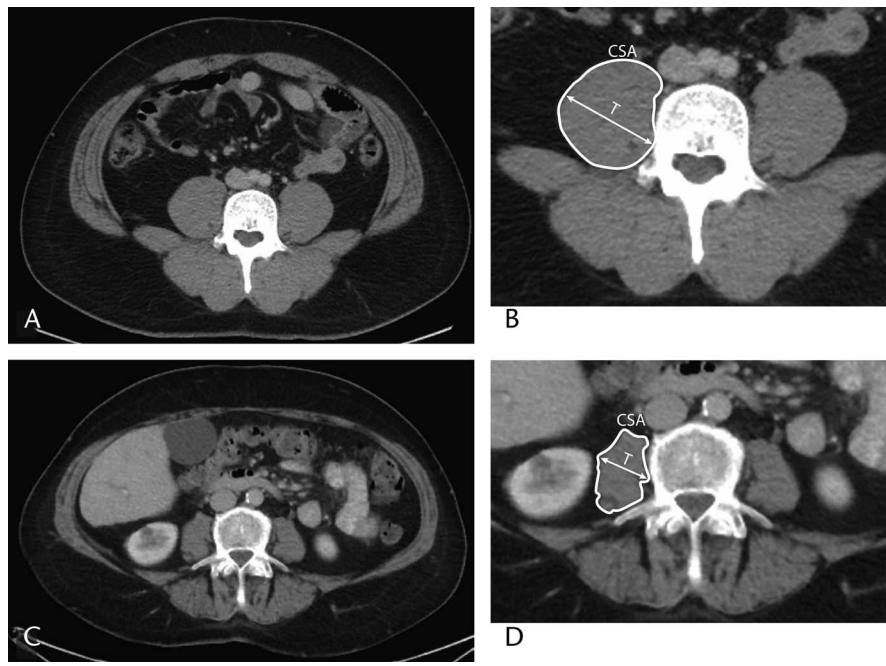

FIGURE 1. Measurement of psoas muscle thickness and CSA at the fourth lumbar level on a CT image. A and B, Patient with normal muscle mass. C and D, Patient with sarcopenia.

TABLE 1. Demographic and Clinical Characteristics of the Study Cohort (N = 265)

Demographics	
Sex, male, n (%)	189 (71)
Age, mean (SD), y	54.3 (12.7)
Disease characteristics, n (%)	
Alcoholic etiology	164 (62)
PERT	128 (48)
Diabetes	93 (35)
Opioid based pain treatment	58 (22)
Pancreatic calcifications	163 (62)
CT assessment parameters, mean (SD)	
SMI, cm^2/m^2	45.8 (9.3)
Psoas, mm/m	15.4 (4.2)
Psoas CSA, cm^2/m^2	3.3 (1.0)

Version 15.1 (StataCorp LP, College Station, Tex) was used for statistical calculations.

RESULTS

We screened medical records from 302 patients with CP for inclusion, of whom 265 were included in the study. Reasons for exclusion were as follows: patients with a CT scan not suitable for segmentation (n = 23), patients with missing information on height (n = 5), patients with missing data on disease characteristics (PERT: n = 6 and diabetes: n = 3). No patients had active cancer or signs of decompensated chronic liver disease. Demographic and disease characteristics of the study cohort are reported in Table 1.

Prevalence of Sarcopenia and Associated Risk Factors

Fifty-four of 265 patients had sarcopenia, which corresponds to a prevalence of 20.4% (95% CI, 15.7%–25.7%). Sarcopenia was significantly associated with age (P = 0.047), PERT (P = 0.04), and opioid treatment (P = 0.03) on univariate analysis. Multivariate analysis confirmed the independence and significance of the association for age (OR, 1.3; 95% CI, 1.1–15.1; P = 0.031) and opioid treatment (OR, 2.36; 95% CI, 1.20–4.64; P = 0.013) (Table 2).

Diagnostic Utility of Psoas Muscle Parameters for Detection of Sarcopenia

Significant associations were observed between psoas muscle thickness and SMI (ρ = 0.62, $P < 0.001$), as well as between the psoas muscle CSA and SMI (ρ = 0.74, $P < 0.001$) (Fig. 2). The psoas muscle thickness was decreased in patients with sarcopenia compared with their nonsarcopenic counterparts (12.4 [SD, 3.4] vs 16.1 [SD, 4.0] mm/m; $P < 0.001$). Likewise, the psoas muscle CSA was decreased in sarcopenic patients (2.5 [SD, 0.8] vs 3.5 [SD, 1.0] cm^2/m^2; $P < 0.001$).

The optimal psoas muscle thickness cutoff for diagnosing sarcopenia was 15.2 mm/m in males and 13.5 mm/m in females. The optimal psoas muscle CSA cutoff for diagnosing sarcopenia was 3.3 cm^2/m^2 in males and 2.5 cm^2/m^2 in females. The associated diagnostic performance characteristics are reported in Table 3; overall acceptable sensitivities were seen for both psoas muscle parameters (>75%), whereas specificities were generally low. To aid in the interpretation of psoas muscle parameters and facilitate easy clinical implementation, we created sex-specific prediction plots to determine the probability of sarcopenia as a function of psoas muscle thickness (Fig. 3).

DISCUSSION

In a large cohort of CP patients, we investigated the diagnostic utility of a simple CT-based method for sarcopenia case finding. The method was based on measurements of psoas muscle thickness and CSA on a standard axial CT image at the fourth lumbar level. Sex-specific cutoffs for height-adjusted psoas muscle thickness and CSA showed acceptable diagnostic performance for detection of sarcopenia, with comparable diagnostic performance for the 2 parameters. Older age, PERT, and opioid treatment were confirmed as risk factors for sarcopenia. Our findings have practical clinical implications: first, we suggest that CP patients, in particular those with risk factors for sarcopenia including PERT and opioid treatment, are systematically screened for sarcopenia. Second, we propose that assessment of psoas muscle thickness and/or CSA on a standard abdominal axial CT image can be used as an initial step in the assessment of sarcopenia. Preferable this initial assessment should be followed by a more detailed nutritional examination, including measures of muscle function if sarcopenia is suspected.

Prevalence of Sarcopenia

The prevalence of sarcopenia was approximately 20% in the present study. This is in line with a recent study form our group (with some overlap with the present study population) where a sarcopenia prevalence of 17% was found.[6] In that study, a more detailed evaluation of muscle mass and function was performed including assessment of body composition, muscle strength, and muscle function using bioelectrical impedance and a dynamometer. Notwithstanding the differences in methodology between studies, the prevalence estimates were remarkably similar, thus

TABLE 2. Univariate and Multivariate Analysis of Risk Factors Associated With Sarcopenia in Patients With CP (N = 265)

			Univariate		**Multivariate**	
	Sarcopenia (n = 54)	**No Sarcopenia (n = 211)**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Sex, male, n (%)	38 (70)	151 (72)	0.94 (0.49–1.82)	0.86		
Age, mean (SD), y*	57.4 (13.9)	53.5 (12.3)	1.27 (1.00–1.61)	0.047	1.31 (1.03–1.67)	0.031
Alcoholic etiology, n (%)	33 (61)	131 (62)	0.95 (0.51–1.75)	0.86		
PERT, n (%)	33 (61)	95 (45)	1.92 (1.04–3.53)	0.036		
Diabetes, n (%)	15 (28)	78 (37)	0.66 (0.34–1.27)	0.21		
Opioid treatment, n (%)	18 (33)	40 (19)	2.14 (1.10–4.15)	0.025	2.36 (1.20–4.64)	0.013

*Odds ratio per decade.

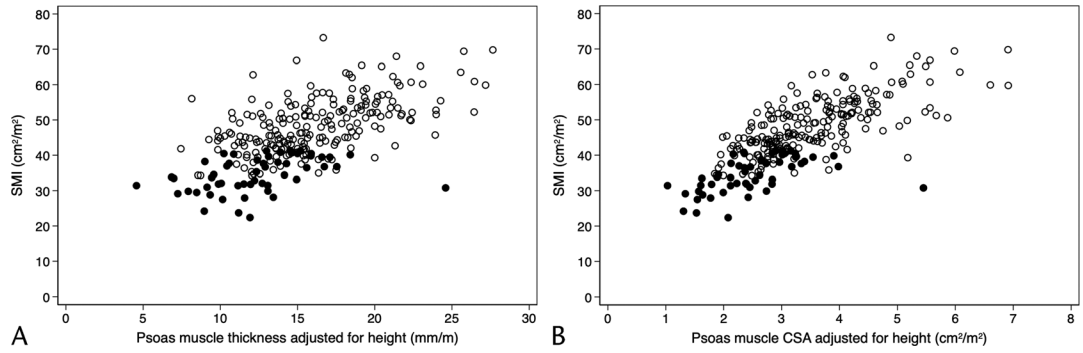

FIGURE 2. A, Correlation between height-adjusted psoas muscle thickness and SMI. B, Correlation between height-adjusted psoas muscle CSA and SMI. Black circles represent female patients and hollow circles represent male patients with CP.

underlining the validity of the CT-based method proposed in the present study. Except for the previously mentioned study, there are a limited number of studies focusing on sarcopenia in CP. In a pilot study from Ireland, 15 (52%) of 29 patients were characterized as sarcopenic using a CT-based assessment of skeletal muscle mass comparable with the method used in the present study.[17] However, no exact cutoffs for the definition of sarcopenia were reported, which makes a direct comparison with our study difficult. Similarly, Bulanova et al[18] reported a prevalence of sarcopenia of 62% in 29 CP patients, who underwent pancreatic surgery. In that study, sex-specific cutoff values of 52.4 cm^2/m^2 for males and 38.5 cm^2/m^2 for females were used to define sarcopenia. These thresholds are probably too high based on recent published population-derived thresholds (as used in the present article) to define sarcopenia, which explain the high prevalence of sarcopenia. In addition, patients referred for surgery may present a selected group of patients with advanced stages of CP, who will be at a higher risk of sarcopenia compared with the patients included in our study.

Risk Factors for Sarcopenia

Pancreatic enzyme replacement therapy (a surrogate marker of exocrine pancreatic insufficiency) was confirmed as a risk factor for sarcopenia in the present study. This finding is in agreement with a previous study by Shintakuya et al[2] and a recent publication from our group.[6] However, as several patients lose weight and decrease physical activity early in their disease course, and typically before evolution of exocrine pancreatic insufficiency, additional risk factors are likely of significance. For example, worsening of chronic abdominal pain after meals, as typically seen in patients with CP, may constraint food intake and limit physical activity. This again may result in weight loss, muscle wasting, and ultimately the development of sarcopenia. Along this line, opioid treatment, a surrogate marker for chronic abdominal pain, was identified as an independent risk factor for sarcopenia. This was also observed in previous studies from our group.[6,19] In addition, opioid treatment has been associated with anorexia and a number of gastrointestinal adverse effects, which may further explain the association between opioid treatment and risk of sarcopenia.[20]

Utility of Psoas Muscle Parameters for Detection of Sarcopenia

In the present study, sex-specific cutoffs for height-adjusted psoas muscle thickness and CSA showed acceptable diagnostic performance for detection of sarcopenia. Hence, the method will be primarily useful for ruling in sarcopenia (rather than ruling out), but because of limited specificity, an additional nutritional workup should be used to confirm the presence of sarcopenia. There are no comparable studies in patients with CP with which to compare the cutoffs derived for psoas muscle parameters. However, the assessment of psoas muscle parameters as surrogate markers for muscle mass and sarcopenia has been widely used in patients with other chronic diseases.[21] In a study of patients with chronic liver disease on the waiting list for liver transplantation, Durand et al[9] measured psoas muscle thickness as a surrogate for muscle mass. Only the transversal diameter of the height-adjusted psoas muscle was associated with waiting list mortality using a cutoff value 16.8 mm/m with no specification for sex. This estimate is close to the sex-specific estimates obtained from the present study and support the notion that psoas muscle thickness may be used as a simple and practical surrogate marker for muscle mass. In another study, Hamaguchi et al[10] analyzed height-adjusted psoas muscle CSA and its impact on mortality in patients with cirrhosis. They suggested a cutoff value of 6.9 cm^2/m^2 for males and 4.1 cm^2/m^2 for females. These estimates are almost twofold the estimates derived from the present study (3.3 and 2.5 cm^2/m^2, respectively) but support that sex differences

TABLE 3. Sex-Specific Thresholds and Performance Characteristics of Cross-sectional CT Assessment Parameters for the Diagnosis of Sarcopenia

CT Assessment Parameter	Sex	Optimal Threshold	ROC AUC (95% CI)	Sensitivity, %	Specificity, %	Correctly Classified, %	LR+	LR−
Psoas thickness	Male	15.2 mm/m	0.75 (0.66–0.83)	76.3	60.3	63.5	1.92	0.39
	Female	13.5 mm/m	0.84 (0.74–0.94)	93.8	63.3	79.7	2.56	0.10
Psoas CSA	Male	3.3 cm^2/m^2	0.80 (0.72–0.88)	84.2	61.6	66.1	2.19	0.26
	Female	2.5 cm^2/m^2	0.88 (0.78–0.97)	81.4	85.0	84.2	5.42	0.22

AUC indicates area under the receiver operating characteristics curve; LR+, positive likelihood ratio; LR−, negative likelihood ratio.

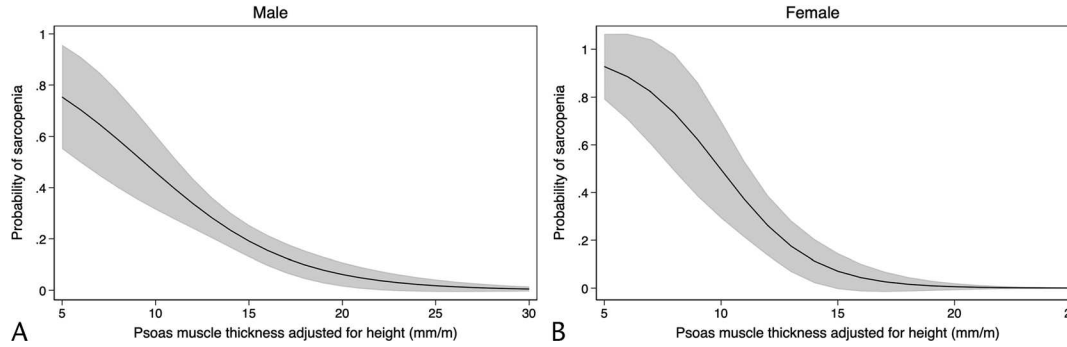

FIGURE 3. Sarcopenia risk as a function of height-adjusted psoas muscle thickness for male (A) and female (B) patients with CP. Shaded areas indicate 95% CIs.

need to be taken into consideration. The observed differences in sex-specific cutoffs between studies are likely related to the different patient populations under investigation (cirrhosis vs CP) as well as the different end points used for threshold derivation (normal reference values vs waiting list mortality). In addition to chronic liver disease, a number of studies in cancer patients including colorectal cancer[11,12] and ovarian cancer[13] have used psoas muscle parameters for the assessment of muscle mass and detection of sarcopenia. Taken together, these studies support that thresholds for sarcopenia differ between patient populations and thus emphasize that cutoff values for sarcopenia should be derived for specific populations as recently recommended by a European consensus document on sarcopenia.[22]

Study Limitations

Our study has some limitations that deserve mentioning. First, many patients with CP have other comorbidities that may influence the risk of sarcopenia.[23] In the present study, patients with active cancer and signs of decompensated liver disease were not included. However, it was not possible to take all other comorbidities into consideration. Second, our findings should be investigated in an independent cohort to validate the diagnostic performance characteristics for the derived psoas muscle parameter cutoffs. Third, as our study mainly included white patients, future studies should validate psoas muscle thresholds for patients with other ethnic backgrounds. Finally, the optimal end point for the definition of sarcopenia still needs to be determined. In the present study, sarcopenia was defined according to normative reference values for SMI derived from a large healthy control population. However, disease-related outcomes, such as mortality or hospitalization burden, may provide a more clinically relevant end points for the definition of sarcopenia. As such, prospective studies based on clinical outcomes should be undertaken to further validate the utility of the proposed psoas muscle thresholds. Furthermore, the utility of psoas muscle parameters for assessment of nutritional treatment responses needs to be clarified.

CONCLUSIONS

Psoas muscle thickness or CSA measured on a standard axial CT slice can be used as surrogates for muscle mass in patients with CP. Used in combination with clinical risk factors, including exocrine pancreatic insufficiency and opioid treatment, the method provides a clinically useful means for detection of sarcopenia in this context.

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